BRETYLIUM AND DOBUTAMINE IN THE TREATMENT OF CORONARY ARTERY DISEASE*

WILLIAM H. FRISHMAN, M.D.

Division of Cardiology, Department of Medicine
Albert Einstein College of Medicine
Bronx, New York

Teaching Scholar
American Heart Association

Two new cardiovascular drugs released this year are important to practicing anesthesiologists. Bretylium tosylate (Bretytol®) is an antiarrhythmic agent useful in refractory ventricular tachyarrhythmias. Dobutamine (Dobutrex®) is a synthetic vasoactive catecholamine useful for myocardial dysfunction. The clinical pharmacology and therapeutic applications of these two exciting new drugs will be discussed.

Bretylium

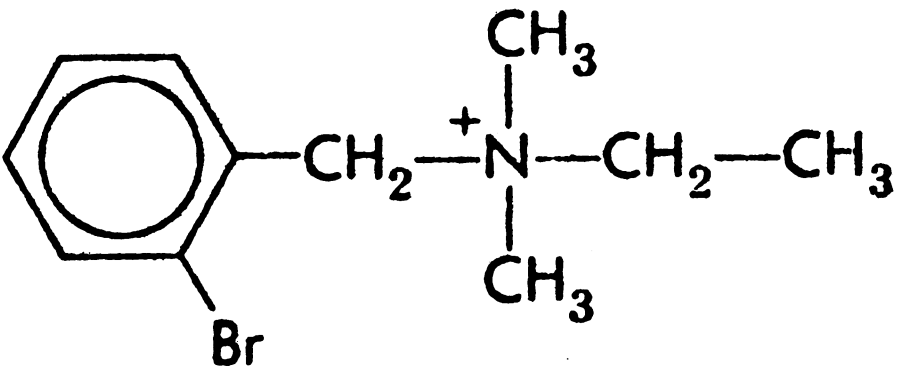
Bretylium tosylate is a pharmacologically unique antiarrhythmic agent recently released for treatment of ventricular tachycardia or ventricular fibrillation. Initially introduced more than 20 years ago as an antihypertensive agent, it was a prototype for a new class of drugs of which guanethidine became the best known. Adverse effects limited the clinical usefulness of bretylium and it soon fell into disfavor as an antihypertensive drug. Ten years ago the drug was found to have antiarrhythmic properties specifically useful for refractory ventricular tachyarrhythmias.

PHARMACOLOGY

Bretylium (Figure 1) is a quartenary ammonium compound with complex pharmacologic actions.[1] It increases the fibrillation threshold of both normal and ischemic tissue in animals and prevents many experimentally-induced arrhythmias. Bretylium accumulates in postganglionic adrenergic

*Presented as the Barbara Lipton Memorial Lecture of the Section on Anesthesiology and Resuscitation of the New York Academy of Medicine on March 7, 1979.

This study was supported by Training Grant HL 07071-72 from the National Heart and Lung Institute. Bethesda, Maryland.



Bretylium

Fig. 1. Newer pharmacologic aspects in coronary artery disease: bretylium and dobutamine.

neurons and initially stimulates release of norepinephrine but subsequently the drug prevents further release of norepinephrine and acts as a sympathetic blocker. It is not known whether the antiarrhythmic effects of bretylium are related to catecholamine blocking properties or to intrinsic electrophysiological increases of the cardiac action potential duration and effective refractory period without change in heart rate.

The onset and duration of action of bretylium are extremely variable but rapid onset of action is usually possible with intravenous administration. Between 70 and 80% of an intravenous dose of bretylium is excreted unchanged in the urine during the first 24 hours after administration.[2] The prolonged duration of action reported in some cases may be due to decreased clearance because of reduced renal function. Bretylium has a positive inotropic effect on the myocardium but it is not yet certain whether this effect is direct or is mediated by catecholamine release. An initial small increase in heart rate sometimes occurs. Ventricular hemodynamics are well preserved following bretylium administration to patients with acute myocardial infarction.

Indications

For patients with severe hemodynamic compromise due to ventricular tachycardia or ventricular fibrillation, the treatment of choice is cardiover-

sion and correction of such contributing metabolic abnormalities as hypokalemia or acidemia and administration of lidocaine or procainamide. For patients with acute myocardial infarction or premature ventricular contractions or tachycardia requiring less urgent treatment, intravenous lidocaine is usually safe and effective, but large doses may be required.[3] If lidocaine is contraindicated or ineffective, procainamide may be given.

Bretylium is indicated for the treatment of life-threatening ventricular arrhythmias, principally ventricular fibrillation and ventricular tachycardia, that have failed to respond to adequate doses of a first-line antiarrhythmic agent such as lidocaine or procainamide. At present, bretylium should not be considered a first-line antiarrhythmic agent. Bretylium should be limited to intensive care units, coronary care units, or other facilities where equipment and personnel for constant monitoring of cardiac arrhythmias and blood pressure are available. Following injection of bretylium, the onset of antiarrhythmic action may be delayed 20 minutes to two hours although it appears to act within minutes in ventricular fibrillation. The delay in onset of action appears to be longer after intramuscular than after intravenous injection.

Multiple clinical trials have tested bretylium in ventricular tachyarrhythmias, but controlled trials are difficult to conduct in the crisis atmosphere surrounding a life-threatening arrhythmia. Most studies have indicated that bretylium can stabilize cardiac rhythm in about half of patients with persistent ventricular fibrillation or recurrent ventricular tachycardias that do not respond to other treatment.[4-7]

Adverse Effects

Bretylium was originally used as an antihypertensive agent, and its most consistent and troublesome adverse effect is hypotension from sympathetic blockade. Hypotension is usually orthostatic and is generally not a problem if the patient remains supine. Hypotension could also develop in the supine position, however, particularly in patients with severely compromised cardiac function, and may persist despite administration of fluids and vasopressors.[8,9] Another potentially serious adverse effect has been a transient increase in heart rate, rise in blood pressure, and worsening of some arrhythmias following initial doses of bretylium, probably from release of neuronal norepinephrine. Until sympathetic blockade is evident, patients should be observed closely after each dose of bretylium for possible worsening of the arrhythmia. Intravenous bretylium often causes

nausea and vomiting that can be minimized by giving the drug over 10 to 30 minutes. Hypersensitivity to infused catecholamines may occur due to bretylium-induced blockade of their uptake at postganglionic sympathetic terminals; both the hypersensitivity to vasopressors and the release of catecholamines that bretylium initially stimulates can aggravate digitalis toxicity. Severe aortic stenosis or severe pulmonary hypertension may prevent an increase in cardiac output to compensate for the peripheral vasodilation that bretylium causes, and bretylium should be used for patients with these conditions only when absolutely necessary.

Dosage and Administration

Bretylium is to be used clinically only for life-threatening ventricular arrhythmias under constant electrocardiographic monitoring. Because there is delay in onset of its antiarrhythmic action, bretylium is not to be considered or used as a replacement for rapidly acting antiarrhythmic agents currently in use. The clinical use of bretylium is only for the short term. The patient should either be kept supine during bretylium therapy or be closely observed for postural hypotension. The optimal dose schedule for parenteral administration of bretylium has not been determined. There is comparatively little experience with dosages greater than 30 mg./kg./day, although such doses have been used without apparent adverse effects. The following schedule has been suggested:

For ventricular fibrillation, an initial rapid intravenous dose of 5 mg./kg. of undiluted bretylium is recommended, with additional doses of 10 mg./kg. up to a total of 30 mg./kg. if necessary. For life-threatening ventricular tachycardia the drug can be infused slowly intravenously (over 10 or more minutes) diluted in glucose or saline solution, or the undiluted drug can be given intramuscularly in a dose of 5-10 mg./kg. Few data are available, however, on the adequacy of absorption after intramuscular injection. The recommended dose for maintenance therapy is 5-10 mg./kg. every six hours, either as an infusion over 10 to 30 minutes or by intramuscular injection. Continuous infusion of 1-2 mg./min. offers maximum control and is considered preferable. Bretylium should be tapered and discontinued after three to five days and long-term oral therapy instituted with other drugs. Although the manufacturer has recommended dosage reduction in patients with impaired renal function, no data are yet available to guide dosage for such patients.

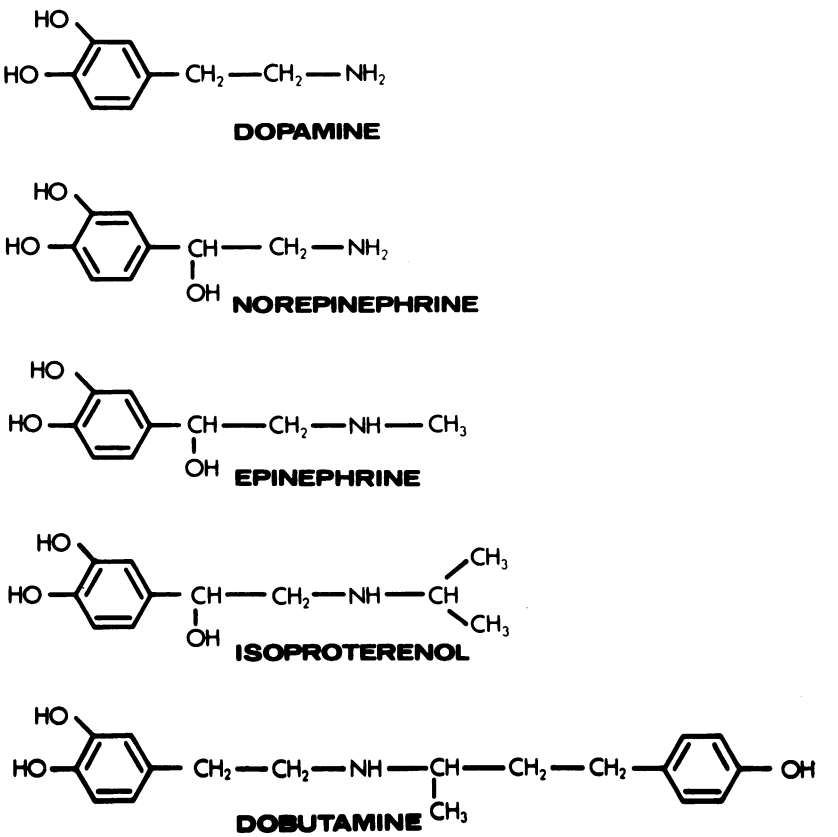


Fig. 2. Newer pharmacologic aspects in coronary artery disease: bretylium and dobutamine. Reproduced by permission from Sonnenblick, E.D., Frishman, W., and LeJentel, T.H.: Dobutamine: A new synthetic cardioactive sympathetic amine. *N. Engl. J. Med. 300:*17-22, 1979.

Conclusion

Bretylium is an effective agent in the treatment of life-threatening ventricular arrhythmias, and is currently the only agent available for chemical conversion of ventricular fibrillation. Bretylium should still be reserved for patients refractory to other types of therapy, and used only in hospital facilities that can provide constant monitoring of blood pressure and cardiac rhythm.

Dobutamine

Dobutamine is a new, synthetic, intravenously administered catechol-

TABLE I. SOME RECEPTOR ACTIONS OF CATECHOLAMINES

Adrenergic receptor	*Site*	*Action*
β_1	Myocardium	Increase atrial and ventricular contractility
	Sinoatrial node	Increase heart rate
	Atrioventricular conduction	Enhance conduction
β_2	Arterioles	Vasodilatation
	Lungs	Bronchodilatation
α	Peripheral arterioles	Vasoconstriction

Reproduced by permission from Sonnenblick, E.H., Frishman, W.H., and LeJemtel, T.H.: Dobutamine: A new synthetic cardioactive sympathetic amine. *N. Engl. J. Med. 300:*17-22, 1979.

amine that acts directly to increase myocardial contractility without inducing marked tachycardia or greatly changing peripheral arterial resistance. These features make it useful for treating acute cardiac failure characterized by low cardiac output and elevated diastolic filling pressure. In July of 1978 it was approved for clinical use in this country.

CLINICAL PHARMACOLOGY

Depending on their structures (Figure 2), catecholamines activate receptors other than cardiac β_1-adrenergic receptors (Table I). β_2-adrenergic receptors mediate vasodilation in the peripheral vasculature and bronchodilation in the lungs. α-adrenergic receptors in peripheral vessels mediate arterial vasoconstriction in opposition to the effects of β_2-adrenergic receptors. The net effect of any of the amines shown in Figure 1 depends on their dominant receptor activity (Table II). Dobutamine acts directly as an intotropic agent whose primary activity results from stimulation of the β_1 receptors of the heart while producing comparatively mild chronotropic, hypertensive, arrhythmogenic, and vasodilatative effects.[10] It does not cause the release of endogenous norepinephrine as does dopamine.[11] In animal studies, dobutamine increases heart rate and decreases peripheral vascular resistance less for a given inotropic effect than does isoproterenol.[12,13]

In patients with decreased cardiac function, both dobutamine and isoproterenol increased the cardiac output to a similar degree.[14] In the care of dobutamine, this increase is usually not accompanied by marked in-

TABLE II. ADRENERGIC-RECEPTOR ACTIVITY OF SYMPATHOMIMETIC AMINES

	α *Peripheral*	β_1 *Cardiac*	β_2 *Peripheral*
Norepinephrine	++++	++++	0
Epinephrine	++++	++++	++
Dopamine*	++++	++++	++
Isoproterenol	0	++++	++++
Dobutamine	+	++++	++
Methoxamine	++++	0	0

*Causes renal and mesenteric dilatation by stimulating dopaminergic receptors.

Reproduced by permission from Sonnenblick, E.H., Frishman, W.H., and LeJemtel, T.H.: Dobutamine: A new synthetic cardioactive sympathetic amine. *N. Engl. J. Med. 300:*17-22, 1979.

crease in heart rate, although tachycardia is occasionally observed, and the cardiac stroke volume is usually increased. In contrast, isoproterenol increases the cardiac index primarily by increasing the heart rate while stroke volume changes little or declines.[15] Dobutamine increases sinus-node automaticity and enhances atrioventricular nodal and intraventricular conduction.[16] However, when given in amounts having similar inotropic effects, dobutamine, like dopamine, increases the sinus-node rate less than isoproterenol while enhancing atrioventricular and intraventricular conduction to a similar extent.[11,17] Systemic vascular resistance is usually decreased by administration of dobutamine. Occasional minimal vasoconstriction has been observed.

Dobutamine, like dopamine, requires continuous intravenous administration. Its plasma half-life in man is two minutes. The drug is eliminated in the body by biotransformation in the liver to inactive glucuronide conjugates and 3-0-methyldobutamine. Most of these metabolites are excreted in the urine and a small percentage in the feces. Biliary excretion with subsequent reabsorption may occur, but has not yet been demonstrated in man.[18]

In summary, dobutamine acts primarily on adrenergic β_1 receptors, whereas β_2 and α receptors are only stimulated to a slight degree (Table II). With doses producing similar increments in cardiac contractile force, dobutamine exerts a much weaker β_2-adrenergic action than isoproterenol and a much weaker α-adrenergic action than norepinephrine. Thus, at moderate dose levels augmentation of myocardial contractility is the most prominent action of dobutamine without major changes in arterial pressure or heart rate. At very high doses, tachycardia and a lowering of peripheral

resistance may appear and produce effects resembling those of isoproterenol.

INDICATIONS

Dobutamine is indicated when parenteral therapy is necessary for inotropic support in the short-term treatment of adults with cardiac decompensation due to depressed contractility resulting from either organic heart disease or from cardiac surgical procedures.[10]

Dobutamine causes dose-related increases of cardiac output in patients with varying degrees of heart failure. Intravenous infusion at rates ranging from approximately 2.5 to 15.0 μg./kg./min. induce a progressive increase in cardiac output.[19-22] Pulmonary wedge pressure decreases, reflecting a fall in diastolic filling pressure in the left ventricle. At lower doses the increase in output occurs with little or no change in mean arterial pressure or heart rate. The more severe the failure, the greater the improvement observed. However, at higher dose levels substantial increments in heart rate also occurred.

Studies of patients with low output cardiac failure where the dosages of dobutamine and dopamine were adjusted to produce similar increments in cardiac output demonstrated an increased heart rate with both drugs. Although dobutamine decreased mean arterial and pulmonary wedge pressure, dopamine did not change arterial pressure and increased wedge pressure.[23]

Similar findings were demonstrated in a crossover study of dopamine and dobutamine (2.5 to 10 μg./kg./min.) in patients with congestive heart failure.[24] Dobutamine produced a progressive rise in cardiac output by increasing stroke volume while simultaneously decreasing both systemic and pulmonary vascular resistances and pulmonary capillary wedge pressure. There was no increment in heart rate or premature ventricular contractions at this dose level. As arterial pressure rose with increased doses of dopamine, pulmonary wedge pressure also rose, and the incidence of premature ventricular contractions per minute increased. At doses greater than 6 μg./kg./min. dopamine augmented heart rate. During a 24-hour infusion of each drug only dobutamine produced a sustained increase of stroke volume, cardiac output, urine flow, urine sodium concentration, creatinine clearance, and peripheral blood flow. Renal and hepatic blood flow was not significantly altered by either drug.

In patients who had undergone cardiopulmonary bypass operations

dobutamine was a potent inotropic drug.[25,26] In general, tachycardia was less prominent, and fewer arrhythmias were observed than with the use of isoproterenol. This effect may prove an advantage of dobutamine when used during emergence from cardiopulmonary bypass, when augmentation of cardiac contractility may be necessary for adequate pump function.

The ability of dobutamine to increase cardiac output in heart failure without increasing oxygen needs or reducing coronary flow due to tachycardia has recommended its use in pump failure associated with an acute myocardial infarction.[27] However, data on the subject are very limited. A recent investigation of patients with acute myocardial infarction administered dobutamine at rates ranging from 1 to 40 μg./kg./min. for 24 hours.[28] To evaluate the effects of dobutamine on cardiac performance in myocardial injury, the treated group was compared to control patients matched to anticipated infarct size and to other control patients matched for early ventricular arrhythmias. Dobutamine significantly increased cardiac output and decreased pulmonary capillary wedge pressure without significantly altering heart rate or systemic blood pressure. The extent of myocardial infarction in relation to what was predicted, the frequency of reinfarction, and extension of infarction were similar in control and treated patients. These investigators concluded that dobutamine in doses sufficient to augment ventricular performance after myocardial infarction did not exacerbate myocardial injury or the frequency of ventricular dysrhythmias.

If ventricular failure had been present in all cases, reductions in ischemia might have resulted as discussed above. Thus, dobutamine should be useful in acute infarction when pump failure characterized by low cardiac outputs and elevated ventricular filling pressures is present.

When mild hypotension is present, dobutamine may increase arterial pressure by augmenting cardiac output. However, in cardiogenic shock characterized by severe hypotension and left ventricular failure, an increase in peripheral resistance may also be required to increase arterial pressure to adequate levels. Measurements of arterial and pulmonary wedge pressure should be obtained and adequate volume expanders administered to correct relative hypovolemia. If hypotension still persists, either dopamine in high doses or norepinephrine (Levophed®) may be required rather than dobutamine. It should be recalled that high doses of dopamine resemble norepinephrine in its vasoconstrictive action. Indeed, when moderate to high doses of dopamine have been required to sustain cardiac contractility, nitroprusside has been simultaneously used to offset excessive peripheral

vasoconstriction, which may raise the arterial pressure beyond required levels, adding to the load on an already burdened heart. In this latter circumstance, dobutamine may substitute for the drug combination of dopamine and nitroprusside. The drug is approved for intravenous use, the usual dose being 2.5 to 10 μg./kg./min. Dosages as high as 40 μg./kg./min. have been used.

Adverse Effects

The most serious adverse effects of all the sympathomimetic amines is the precipitation of arrhythmias. The electrophysiological properties of dobutamine are similar to those of isoproterenol, and ventricular arrhythmias have followed both drugs. However, it is claimed that dobutamine causes a lower incidence of arrhythmias as compared with isoproterenol[26] and dopamine.[24] If rapid ventricular rates occur in the presence of obstructive coronary artery disease, ischemia can be induced or worsened, as noted above.

Dobutamine may cause a marked increase in heart rate or systolic blood pressure. Approximately 10% of patients in clinical studies have had rate increases of 30 beats per minute or more, and about 7.5% have had an increase in systolic blood pressure of 50 mm. Hg or more. Reduction of dosage usually reverses these effects promptly. Because dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation may risk development of a rapid ventricular response. Other side effects reported in 1 to 3% of patients include nausea, headache, anginal pain, palpitation, and shortness of breath. No abnormal clinical laboratory values have been attributable to dobutamine. Infusions of up to 72 hours have revealed no adverse effects other than those seen with shorter infusions.

Conclusions

Dobutamine, a synthetic derivative of isoproterenol, directly increases myocardial contractility with less peripheral arterial effects or tachycardia than is seen with other sympathomimetic agents at dose levels causing similar increases in contractility. Administered intravenously, it should be useful for the treatment of relatively acute heart failure uncomplicated by severe hypotension.

REFERENCES

1. Bacaner, M. B.: Quantitative comparison of bretylium with other antifibrillatory drugs. *Am. J. Cardiol. 21:*504-12, 1968.
2. Kuntzman, R., Rsai, I., Chang, R., and Conney, A. H.: Disposition of bretylium in man and rat. *Clin. Pharmacol. Ther. 11:*829-37, 1970.
3. Alderman, E. L., Kerber, R. E., and Harrison, D. C.: Evaluation of lidocaine resistance in man using intermittent large-dose infusion techniques. *Am. J. Cardiol. 34:*342-49, 1974.
4. Dhurandhar, R. W., Teasdale, S. J., and Mahon, W. A.: Bretylium tosylate in the management of refractory ventricular fibrillation. *Can. Med. Assoc. J. 105:*161-65, 1971.
5. Bernstein, J. G. and Koch-Wiser, J.: Effectiveness of bretylium tosylate against refractory ventricular arrhythmias. *Circulation 45:*1024-34, 1972.
6. Sanna, G. and Archidiacono, R.: Chemical ventricular defibrillation of the human heart with bretylium tosylate. *Am. J. Cardiol. 32:*982-87, 1973.
7. Holder, D. A., Sniderman, A. D., Fraser, G., and Fallen, E. L.: Experience with bretylium tosylate by a hospital cardiac arrest team. *Circulation 55:*541-44, 1977.
8. Cohen, H. C., Gozo, E. G., Langendorf, R., et al.: Response of resistant ventricular tachycardia to bretylium. *Circulation 47:*331-40, 1973.
9. Luomanmaki, K., Heikkila, J., and Hartel, G.: Bretylium tosylate: adverse effects in acute myocardial infarction. *Arch. Int. Med. 135:*515-18, 1975.
10. Sonnenblick, E. H., Frishman, W. H., and LeJemtel, T. H.: Dobutamine: A new synthetic cardioactive sympathetic amine. *Drug Ther. 300:*17022, 1979.
11. Tuttle, R. R. and Mills, J.: Dobutamine: Development of a new catecholamine to selectively increase cardiac contractility. *Circ. Res. 36:*185-96, 1975.
12. Bodem, R., Skelton, C. L., and Sonnenblick, E. H.: Inotropic and chronotropic effects of dobutamine on isolated cardiac muscle. *Eur. J. Cardiol. 2:*181-89, 1974.
13. Lumley, P., Broadley, K. J., and Levy, G. P.: Analysis of the inotropic: chronotropic selectivity of dobutamine and dopamine in anaesthetised dogs and guinea-pig isolated atria. *Cardiovasc. Res. 11:*17-25, 1977.
14. Jewitt, D., Birkhead, J., Mitchell, A., and Dollery, C.: Clinical cardiovascular pharmacology of dobutamine; a selective inotropic catecholamine. *Lancet 2:*363-67, 1974.
15. Loeb, H. S., Khan, M., Saudye, A., and Gunnar, R. M.: Acute hemodynamic effects of dobutamine and isoproterenol in patients with low output cardiac failure. *Circ. Shock. 3:*55-63, 1976.
16. Loeb, H. S., Sinno, M. Z., Saudye, A. I., et al.: Electrophysiologic properties of dobutamine. *Circ. Shock. 1:*217-20, 1974.
17. Tuttle, R. R., Hillman, C. C., and Tommey, R. E.: Differential β-adrenergic sensitivity of atrial and ventricular tissue assessed by chronotropic, inotropic and cyclic AMP responses to isoprenaline and dobutamine. *Cardiovasc. Res. 10:*452-58, 1976.
18. Murphy, P. J., Williams, T. L., and Kau, D. L. K.: Disposition of dobutamine in the dog. *J. Pharmacol. Exp. Ther. 199:*423-31, 1976.
19. Loeb, H. S., Kahn, M., Klodnycky, M. L., et al.: Hemodynamic effects of dobutamine in man. *Circ. Shock. 2:*29-35, 1975.
20. Beregovich, J., Bianchi, C., D'Angelo, R., et al.: Haemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure. *Br. Heart J. 37:*629-34, 1975.
21. Akhtar, N., Mikulic, E., Cohn, J. N., and Chaudhry, M. H.: Hemodynamic effects of dobutamine in patients with severe heart failure. *Am. J. Cardiol. 36:*202-05, 1975.

22. Leier, C. V., Webel, J., and Bush, C. A.: The cardiovascular effects of the continuous infusion of dobutamine in patients with severe cardiac failure. *Circulation 56:*468-72, 1977.
23. Loeb, H. S., Bredakis, J., and Gunnar, R. N.: Superiority of dobutamine over dopamine for augmentation of cardiac output in patients with chronic low output cardiac failure. *Circulation 55:*375-81, 1977.
24. Leier, C. V., Heban, P. T., Huss, P., et al.: Comparative systemic and regional hemodynamic effects of dopamine and dobutamine in patients with cardiomyopathic heart failure. *Circulation 58:*466-75, 1978.
25. Tinker, J. H., Tarhan, S., White, R. D., et al.: Dobutamine for inotropic support during emergence from cardiopulmonary bypass. *Anesthesiology 44:*281-86, 1976.
26. Sakamoto, T. and Yamada, T.: Hemodynamic effects of dobutamine in patients following open heart surgery. *Circulation 55:*525-33, 1977.
27. Kirk, E. S., LeJemtel, T. H., Nelson, G. R., and Sonnenblick, E. H.: Mechanisms of beneficial effects of vasodilators and inotropic stimulation in the experimental failing ischemic heart. *Am. J. Med. 65:*189-96, 1978.
28. Gillespie, T. A., Ambas, H. D., Sobel, B. E., and Roberts, R.: Effects of dobutamine in patients with acute myocardial infarction. *Am. J. Cardiol. 39:*588-94, 1977.